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Myocardial Amiodarone and Desethylamiodarone Concentrations in Patients Undergoing Cardiac Transplantation

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Myocardial amiodarone and desethylamiodarone concentrations were measured at multiple sites in the explanted heart in four patients who underwent cardiac transplantation. Patients were taking amiodarone, 200 to 400 mg/day (mean 300 ± 115), for 88 to 428 days (mean 229 ± 148). The mean cumulative dose was 58 ± 21.3 g. Plasma amiodarone concentration in three subjects was 204, 312 and 419 ng/ml and desethylamiodarone concentration was 268, 513 and 880 ng/ml, respectively.

Significant interindividual variability in myocardial concentrations of amiodarone and desethylamiodarone was observed ($p < 0.05$). Mean myocardial amiodarone concentration ranged from 4 ± 1.0 to 29 ± 17.2 μg/g ($p < 0.05$); mean desethylamiodarone concentration ranged from 22 ± 8.8 to 141 ± 102. 5 μg/g ($p < 0.05$). At each site, save for fat, myocardial desethylamiodarone concentration was higher than amiodarone concentration. Greater intraindividual variability was observed in myocardial desethylamiodarone compared with amiodarone concentration particularly in septal and scar tissue (p = NS).

No significant relation was found between myocardial concentration and duration of treatment. In patients with significant ventricular disease, usefulness of plasma amiodarone and desethylamiodarone concentration to estimate myocardial concentration is limited by intra- and interindividual variability.

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The complex distribution and elimination of amiodarone has been noted in clinical studies evaluating its plasma pharmacokinetics (1,2). For many cardioactive agents drug concentration is significantly higher in myocardium, the site of action, compared with plasma. That this is also the case for amiodarone has been reported in animals (3,4), as well as in single biopsy specimens in humans (5,6). Desethylamiodarone, its major metabolite, is also found in very high concentrations in lung, liver, fat and myocardium (6). Both drugs have important cardiac electrophysiologic effects and desethylamiodarone has even more potent effects on prolongation of the QRS duration, atrial refractory period and ventricular refractory period than the parent compound (7,8). Accumulation of desethylamiodarone has been suggested as a source for the delayed electrophysiologic effect in patients receiving long-term treatment with amiodarone.

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Evaluation of myocardial concentration of parent drug and metabolite could improve our understanding of their electrophysiologic effects and mechanism of action of drug. However, it is unclear whether there is significant variability of parent and metabolite concentrations in the heart. The purpose of this study was 1) to describe amiodarone and desethylamiodarone concentrations at selected sites in the explanted heart, and 2) to examine for intra- and interindividual variability in myocardial concentrations in four patients who underwent cardiac transplantation.

Methods

Myocardial samples. Samples of cardiac muscle from the right and left atria and ventricles were taken at the time of cardiac transplantation from the explanted heart of four patients to measure drug concentration. A stitch was placed on the cephalad aspect of each specimen to identify the site; samples were blotted dry and immediately frozen. Each explanted heart had areas of fibrosis and scar and, in addition, one (Patient 3) had a thinned area in the apex of the left ventricle and another (Patient 4) had a discrete aneurysm. Myocardial samples were selected so that drug concentration could be measured in areas representing central (site A) and peripheral (site B) regions of scar.

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Table 1. Characteristics of Four Patients

Patient No.	Age (yr)/Gender	Daily Amiodarone Dose (mg; mg/kg body weight)	Duration of Treatment (days)	Heart Disease*	RV + LV Weight (g)
1	48/M	200; 2.9	428	CAD, cardiomyopathy, EF 12%	278
2	50/M	400; 3.6	88	CAD, cardiomyopathy, EF 20%	332
3	45/M	200; 2.9	247	Cardiomyopathy, EF 15%, AICD	650
4	47/M	400; 4.7	152	CAD, cardiomyopathy, EF 15%	345
Mean	48	300; 3.5	229		401
±SD	2	115; 1	148		168

*Diagnosis from pathology report. AICD = automatic implantable cardioverter-defibrillator; CAD = coronary artery disease; EF = ejection fraction; LV = left ventricle; M = male; RV = right ventricle.

At the time of analysis myocardial samples were defrosted, blotted, dried and cut. The samples measured approximately 3 × 3 mm and weighed 0.085 ± 0.044 g (range 0.204 to 0.033). After weighing, samples were placed into Ten Broeck tissue grinders with 2 ml of methanol (ACS grade), hand homogenized and transferred to test tubes. The resulting solution was then evaporated to dryness. After evaporation was complete, 0.5 ml of internal standard (3 μg/ml), 1 ml acetate buffer (1 *M*) and 5 ml hexane were added to each test tube. The solution was mixed at low speed for 5 min and then centrifuged for 10 min. The resulting organic layer was transferred to a test tube and evaporated to dryness, reconstituted with 150 μl of mobile phase and 50 μl aliquots were injected into the injection portal.

Plasma samples to measure amiodarone and desethylamiodarone concentrations. These were taken 14 h after the last drug dose on the day of transplant surgery. Plasma samples were measured for amiodarone and desethylamiodarone by combining 1 ml plasma, 1 ml acetate buffer (1 *M*), 20 μl internal standard (80 ng/μl) and 5 ml hexane in a test tube. The solution was mixed at a low speed for 5 min and then centrifuged for 10 min. The resulting organic layer was transferred to a test tube and evaporated to dryness. The contents of the tube were reconstituted with 150 μl of mobile phase and 50 μl samples were injected into the injection portal. The concentration of the plasma samples was determined from a standard curve.

Apparatus. Analyses were performed using a model 440 high performance liquid chromatograph (Waters Associates) interfaced with a 740 Data Module. An M45 solvent delivery system and a U6k injector were employed. Chromatography was performed using a Millipore Z Module radial compression separation system with a CN 10 μm (5 mm × 10 cm) Radial Pak cartridge (Waters Associates). The flow rate was 1.0 ml/min operating at a pressure <1,500 psi. The detector wavelength was set at 254 nm.

Mobile phase. The mobile phase consisted of 0.05 *M* perchloric acid ($HClO_4$) and Acetonitrile (HPLC grade) (50:50) plus 1 *M* heptane sulfonate (5 ml/liter of mobile phase). The solution was made daily, filtered and degassed. The flow rate was 1 ml/min with a pressure <1,500 psi.

Statistical analysis. Repeated measures of analysis of variance were used to test the null hypothesis that there is no difference between amiodarone and desethylamiodarone concentrations at sites throughout the heart and among patients. Data were normalized for dose size and are expressed as range and mean value ± SD. A p value <0.05 was considered significant.

Results

Patient characteristics (Table 1). All four patients had reduced ejection fraction (range 12% to 20%, mean 16 ± 3.3%) and were diagnosed as having cardiomyopathy: three had coronary artery disease and one had normal coronary arteries. All patients were men and ranged in age from 45 to 50 years (mean 48 ± 2) and were taking amiodarone, 200 to 400 mg/day (mean 300 ± 115) for 88 to 428 days (mean 229 ± 148). The mean cumulative daily dose (daily dose × duration of treatment) was 58 ± 21.3 g: 85.6, 35.2, 49.2 and 60.8 g, respectively, in patients 1 to 4. Patients 2, 3 and 4 were also taking digoxin.

All four patients had a malignant ventricular arrhythmia as the indication for starting amiodarone therapy: ventricular tachycardia at a rate of 140 to 160, 200 to 210 and 140 to 150 beats/min, respectively, in Patients 1, 2 and 4, and cardiac arrest with recurrent ventricular tachycardia requiring an automatic implantable defibrillator in Patient 3.

Plasma drug concentrations (Table 2) measured before explantation for Patients 1, 2 and 3, respectively, were 419, 204 and 312 ng/ml for amiodarone and 513, 268 and 880 ng/ml

Table 2. Amiodarone and Desethylamiodarone Myocardial Concentration in Four Patients

	Patient No.						
	1	(ratio)*	2	(ratio)*	3	(ratio)*	4
Tissue amiodarone (μg/g)							
Atrium							
Right	9	(21)	3	(15)	11	(35)	—
Left	11	(26)	4	(20)	12	(38)	—
Ventricle							
Right	5	(12)	3	(15)	14	(45)	—
Left	6	(14)	4	(20)	16	(51)	45
Septum							
High	5	(12)	4	(20)	13	(42)	49
Low	3	(7)	4	(20)	8	(26)	23
Scar							
Central (A)	6	(14)	6	(29)	6	(19)	8
Peripheral (B)	7	(17)	3	(15)	6	(19)	22
Mean ± SD	7 ± 2.5	(15 ± 6)	4 ± 1.0	(19 ± 5)	11 ± 3.7	(34 ± 12)	29 ± 17.2
Fat							
Right ventricle	275	(656)	32	(157)	125	(401)	—
Left ventricle	151	(360)	17	(83)	218	(699)	—
Plasma amiodarone (ng/ml)	419		204		312		—
Amiodarone dose (mg/kg body weight)	2.9		3.6		2.9		4.7
Tissue desethylamiodarone (μg/g)							
Atrium							
Right	40	(78)	15	(56)	31	(35)	—
Left	30	(58)	19	(71)	39	(44)	—
Ventricle							
Right	22	(42)	19	(71)	63	(72)	—
Left	31	(60)	14	(52)	69	(78)	214
Septum							
High	26	(50)	25	(93)	55	(63)	279
Low	18	(35)	34	(127)	30	(34)	104
Scar							
Central (A)	12	(23)	37	(138)	24	(27)	29
Peripheral (B)	28	(55)	16	(60)	22	(25)	80
Mean ± SD	26 ± 8.6	(50 ± 17)	22 ± 8.8	(84 ± 33)	42 ± 18.3	(47 ± 21)	141 ± 102.5
Fat							
Right ventricle	90	(174)	21	(78)	39	(44)	—
Left ventricle	42	(81)	15	(56)	74	(84)	—
Plasma desethylamiodarone (ng/ml)	513		268		880		—

*Numbers in parentheses are ratio of tissue concentration to plasma concentration.

for desethylamiodarone. In Patient 4 plasma samples and myocardial samples from atria, left ventricle and fat were not assessed because of a power failure during freezer storage that resulted in spoiled samples.

Amiodarone myocardial concentration (Table 2). At pathologic examination explanted myocardium consisting of right and left ventricle weighed 278 to 650 g (mean 401 ± 168). At transplantation the atria were not entirely surgically removed, thus accounting for the relatively normal heart weight for Patients 1, 2 and 4. Significant interindividual variability in myocardial amiodarone concentration was observed ($p < 0.05$) even when normalized for dose size ($p < 0.05$). There was no significant relation between concentration and cumulative dose. The following ranges of myocardial amiodarone concentration (μg/g) were noted: right atrium, 3 to 11 (mean 8 ± 4); left atrium, 4 to 12 (mean 9 ± 4); right ventricle, 3 to 14 (mean 7 ± 6); left ventricle, 4 to 45 (mean 18 ± 19); high septum, 4 to 49 (mean 18 ± 21); low septum, 3 to 23 (mean 10 ± 9); scar site A, 6 to 8 (mean 7 ± 1); scar site B, 3 to 22 (mean 10 ± 9); fat adherent to right ventricle, 32 to 275 (mean 144 ± 123); fat adherent to left ventricle, 17 to 218 (mean 129 ± 102). Myocardial amio-

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darone concentration was greater than plasma concentration and this ratio ranged from 7 to 51 (mean 23 ± 11). Amiodarone concentration was highest in fat and, consequently, the fat to plasma amiodarone ratio was higher, 83 to 699 (mean 393 ± 251).

Plasma amiodarone concentration did not reflect myocardial amiodarone concentration, as illustrated by two patients taking the same dose, 2.9 mg/kg body weight per day. Patient 1, who had an amiodarone plasma concentration of 419 ng/ml, had a low myocardial amiodarone concentration ranging from 3 to 11 μg/g (ratio 7 to 26). In contrast, the plasma amiodarone concentration of Patient 3 was lower (312 ng/ml), but the myocardial amiodarone concentration was higher (range 6 to 16 μg/g) (ratio 19 to 51) (Table 2). In these two patients plasma desethylamiodarone concentrations, 513 and 880 ng/ml, respectively, were associated with high myocardial metabolite concentrations: 1) range 12 to 40 μg/g (ratio 23 to 78) for Patient 1, and 2) range 22 to 69 μg/g (ratio 25 to 78) for Patient 3.

Desethylamiodarone myocardial concentration (Table 2). As with amiodarone, there was interindividual variability in myocardial desethylamiodarone concentration ($p < 0.05$) and no relation between concentration and cumulative dose. Myocardial desethylamiodarone concentration was higher than amiodarone concentration at each site except for fatty tissue. Intraindividual variability was greater for desethylamiodarone than for amiodarone, as noted by the wider standard deviation; however, this difference was not statistically significant. The following ranges of myocardial desethylamiodarone concentrations (μg/g) were noted: right atrium, 15 to 40 (mean 29 ± 14); left atrium, 19 to 39 (mean 29 ± 10); right ventricle, 19 to 63 (mean 35 ± 26); left ventricle, 14 to 214 (mean 82 ± 91); high septum, 25 to 279 (mean 96 ± 123); low septum, 18 to 104 (mean 47 ± 39); scar site A, 12 to 37 (mean 26 ± 10); scar site B, 16 to 80 (mean 37 ± 29); fat adherent to right ventricle, 21 to 90 (mean 50 ± 36); fat adherent to left ventricle, 15 to 74 (mean 44 ± 30). Myocardial desethylamiodarone concentration was greater than plasma concentration (range 12 to 69 μg/g; ratio range 23 to 138).

Scar. In accord with findings in other sites, desethylamiodarone concentration in scar was higher (mean 31 ± 21 μg/g) than that of amiodarone (mean 8 ± 6 μg/g). Patient 4, who had a discrete left ventricular aneurysm, had a twofold difference in amiodarone concentration between central and peripheral sites and high and low septal tissue. In addition, there was variability of desethylamiodarone concentration in central and peripheral scar tissue in Patients 1, 2 and 4 and in high and low septal tissue of all patients.

Discussion

The opportunity to characterize myocardial drug concentration of amiodarone and its cardioactive metabolite, desethylamiodarone, was provided by analysis of myocardial samples from four patients who underwent cardiac transplantation. Two previous reports (6,9) presented myocardial amiodarone concentrations in biopsy specimens from the right atrium; this report describes myocardial determinations of amiodarone and desethylamiodarone concentrations from four cardiac chambers. Interindividual variability in plasma and myocardial concentrations in patients taking similar or equivalent (mg/kg) doses was observed ($p < 0.05$). Concordant amiodarone concentration was observed within right and left cardiac chambers. Intraindividual variability was more marked for desethylamiodarone than for amiodarone at all myocardial sites.

Electrophysiologic effects. Both amiodarone and its metabolite have important cardiac electrophysiologic effects and desethylamiodarone has even more potent effects on prolongation of the QRS duration, atrial refractory period and ventricular refractory period than does the parent compound (7,8). Abnormalities of conduction and refractoriness in depressed tissue underlie the mechanism of many arrhythmias, and disparate drug concentration within or near the arrhythmic site could cause further inhomogeneity of conduction or refractoriness accounting for inadequate efficacy or worsening of some arrhythmias. Clinical observations (10), although largely unproved, suggest that arrhythmia suppression is more difficult to achieve and proarrhythmia more likely in patients with significant left ventricular disease and scarring. The observations here, whereby anatomic abnormalities are associated with variable drug concentrations among patients, support the view that the antiarrhythmic effect of amiodarone is more reliably guided by clinical outcome or electrophysiologic testing than by plasma drug concentration (11).

Cationic amphiphilic drugs. Several possibilities to account for the variable drug concentrations among the four patients were considered, including perfusion in and out of myocardial areas sampled, degree of fibrosis, number and extent of drug receptors and binding, and myocardial lipid accumulation. Amiodarone and desethylamiodarone are classified as cationic amphiphilic drugs and, like others of this class, are potent inhibitors of lysosomal phospholipase activity, a primary mechanism whereby phospholipidosis is induced (12). Ultrastructural changes indicate that amiodarone therapy is associated with lamellar inclusion bodies found in lung, liver, lymph nodes and cornea (13). Recently, similar lysosomal inclusion bodies have been identified in the canine myocardium (14) characterized by variable and patchy distribution. Because amiodarone and desethylamiodarone appear to increase in parallel with phospholipid (15), these ultrastructural changes may account for variability in lipid concentration and consequent amiodarone and desethylamiodarone content as well.

Conclusions. Measurement of plasma concentration often is useful for assessing drug effect, particularly when

inadequate or excessive drug concentration is suspected. However, as observed here, drug concentration measured in the plasma may not predict myocardial concentration. A limitation of our study is the small study group consisting of four subjects with severely depressed left ventricular function. It is not clear if the drug variability among these patients observed after oral amiodarone therapy holds for patients with normal or minimally depressed ventricular function or for other antiarrhythmic drugs whose pharmacokinetics differs and is less complex than that of amiodarone. Intra- and interindividual variability in myocardial concentration limits the usefulness of amiodarone and desethylamiodarone plasma drug concentration for predicting drug effect and may account for lack of efficacy or untoward events despite apparent therapeutic plasma concentration.

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